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Summary of Talk at CPAC Rome 2019 Workshop

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"Continuous Biocatalytic Manufacturing Approaches for the Synthesis of Drugs"

Continuous bioprocessing ("Enz-Flow") has become a highly relevant technique to achieve enantioselective transformations. These types of reactions are traditionally catalyzed by metal or organocatalysts that can be expensive, toxic, or involve harsh reaction conditions. Conversely, engineered enzyme bioprocessing can improve process sustainability, affordability, and substrate selectivity. Combining continuous processing technologies with biocatalysis *via* whole-cell immobilization techniques can further improve molecule production while reducing the use of dangerous and expensive chemicals and substantially contributing to demonstrating greener synthetic approaches.

Recent advancements have been reported on the genetic engineering of enzymes (BM3-Hstar and Mb H64V-V68A) to catalyze cyclopropanation reactions like those needed to synthesize precursors to levomilnacipran, which is a cyclopropane-containing active pharmaceutical ingredient prescribed to treat fibromyalgia syndrome and major depressive disorder. The research presented at the CPAC Rome 2019 Workshop establishes two different whole-cell immobilization strategies, calcium alginate encapsulation and quaternary ammonium (QA) adsorption, to increase the versatility of these cyclopropanation reactions as both batch and flow processes. Entrapment of whole-cell biocatalysts with calcium alginate was shown to increase shelf-life while retaining catalytic activity. Continuous bioprocessing of a cyclopropane en route to levomilnacipran was achieved with BM3-Hstar whole cells immobilized on QA, tripling the molar conversion per hour.